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Invited Review

Endoscopic treatment of gastroesophageal varices

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SUMMARY

Variceal bleeding continues to be a leading cause of death in cirrhotic patients. Both vasoactive drugs and endoscopic therapy play a significant role in the acute variceal bleeding setting as well as in primary and secondary prevention of variceal bleeding. All patients with cirrhosis should be screened with endoscopy for varices at diagnosis.

In primary prevention, prophylaxis should be offered in patients with medium and large varices. Although endoscopic variceal ligation seems to be more effective than non-selective beta-blockers in preventing first variceal bleeding it does not improve survival rate. Considering the small number of patients enrolled in the randomized trials, the inability of endoscopic ligation to prevent bleeding from portal gastropathy, the cost and the safety issues related to ligation we recommend beta-blockers as the first line treatment. Endoscopic variceal ligation should be offered to patients with at least medium varices and contraindications or intolerance to beta-blockers. In acute variceal bleeding the treatment of choice is the combination of endotherapy with vasoactive drugs, particularly when administration of drugs started early before endoscopy. Endoscopic sclerotherapy has been shown to reduce bleeding and increase survival, but recently endoscopic ligation has been considered to be superior to sclerotherapy in this setting. The risk of recurrent bleeding and death following an episode of variceal bleeding is very high. In patients who have not received primary prophylaxis the combination of EVL and beta blockers should be used in this setting. In patients who are on beta-blockers for primary prevention EVL should be added. Patients who fail endoscopic and pharmacological treatment should undergo TIPS, surgical shunts or liver transplantation.

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INTRODUCTION

Liver cirrhosis is responsible for 90% of portal hypertension in Europe and North America. Portal hypertension is a life-threatening complication of cirrhosis and results in the development of portosystemic shunts comprising esophageal varices.[1] Gastroesophageal varices develop when portal pressure exceeds 10-12 mmHg. Once esophageal varices have developed, they tend to increase in size and eventually bleed. It is estimated that 60-70% of upper gastrointestinal bleeding episodes in patients with cirrhosis are due to rupture of varices.[2] The mortality rate for variceal bleeding in patients with cirrhosis has been falling during the last decades, and recently it was reported at aproximately 20%[2-4], but it continues to be amongst the leading causes of death in these patients. This reduction has been brought about as a result of the expansion of our knowledge in the pathogenesis of portal hypertension, the use of pharmacologic and endoscopic therapies as well as antibiotic prophylaxis. The evolving role of endoscopy makes a major contribution to the better management of the cirrhotic patient with acute bleeding oesophageal varices as well as in primary and secondary prevention of variceal bleeding.

Primary prevention

At the time of diagnosis of cirrhosis, esophageal varices are present in approximately 30% of patients with well compensated and 60% of patients with decompensated liver disease. Approximately 33% of patients with cirrhosis and esophageal varices will present variceal bleeding within one year following the diagnosis of varices. The risk for the first episode of variceal haemorrhage is higher in patients with severe liver failure, large varices and "red spots" revealed endoscopically. The high bleeding related mortality has led to attempts both to identify high-risk patients for bleeding and to prevent it. Thera-

pies that have been applied include surgery, administration of drugs (non selective beta-blockers, and isosorbide mononitrate) and endoscopic eradication of varices [sclerotherapy (EIS) and banding ligation (EVL)].

All patients with cirrhosis should undergo endoscopic examination at the time of initial diagnosis.[5] The first choice for primary prophylaxis of portal hypertensive bleeding in cirrhosis is the use of selective beta-blockers.[6] Endoscopic sclerotherapy has been abandoned in the primary prevention setting because of increased morbidity and mortality(5;7-10). Endoscopic banding ligation seems to be useful in patients with medium and large esophageal varices.[5]

Metanalysis of 7 randomized trials shows that EVL reduced both the risk of first portal hypertensive bleeding (OR, 0,25 (95% CI, 0,17–0,37) and mortality (OR, 0,42 (95% CI, 0,29–0,60) compared to no treatment,[11] whereas ligation reduced the risk of first bleeding (OR, 0,54 (95% CI, 0,37-0,81), but not mortality (OR 0.97 (95% CI, 0,67-1,42) compared to beta-blockers.[6]

Three trials have been published in this area recently.[12-14] In two, no significant difference between EVL and propranolol was observed (12;14). On the contrary, the third randomized trial by Jutabha et al[13] suggested that propranolol-treated cirrhotics with high-risk oesophageal varices had a significantly higher rate of bleeding from oesophageal varices and greater cumulative mortality than those who had EVL. However, we have challenged this interpretation.[6]

Recently the issue of offering endoscopic treatment with ligation only to patients with large varices and high bleeding risk and not to all patients with varices has been debated.[15]The estimated probability of bleeding within 1 year for Child Pugh grade A patients with large varices and moderate red signs is 24% compared with 20% for Child C patients with small varices and no red signs.Thus, some patients with small varices have a considerable risk of first bleeding.[16]

Another issue of ligation in the primary prevention setting, is the safety of the endoscopic procedure. Therefore, in the trial by Schepke et al[17] bleeding from ligation occurred in 5 patients (6,7%) with one life-threatening and two fatal outcomes. This is in concordance with our results recently published.[11] In this trial EVL versus no treatment was compared in cirrhotics with intolerance or contraindications to b-blockers for prevention of first bleeding. A sample size of 214 patients was planned including all sizes of varices. However the trial was stopped after assessing 52 patients due to increased bleeding in the EVL group. After a mean follow-up period of 19,5 months, 5 patients from the EVL group bled (p= 0.24). In addition, we showned that 60 % of the bleeding in the banding group was probably iatrogenic, requiring the study to be stopped. This is the first study suggesting that EVL may be harmful when used as primary prophylaxis, as was to prophylactic sclerotherapy in the past.

In a recent study[18] assessing the effectiveness of the combination treatment with ligation and beta-blockers in this setting (144 patients, high-risk varices, EVL plus propranolol vs EVL), there was no significant difference in the actual probability of first bleed at 20 months between the two groups. The authors conclude that the addition of propranolol does not decrease the probability of first bleed or death in patients on EVL. However, the recurrence of varices is lower if propranolol is added to EVL.

Recent recommendations at the Baveno IV Consensus Workshop which was held on April 28-29, 2005 include:[5] a) all cirrhotics should be screened for varices at diagnosis, b) EVL is useful in preventing variceal bleeding in patients with medium and large varices, c) EVL is more effective than non-selective beta-blockers in preventing first variceal bleeding but does not improve survival rate, d) EVL should be offered to patients with medium/large varices and contraindications or intolerance to beta-blockers.

The small number of patients enrolled in the above studies in association with the conflicting results and the EVL cost, lead us to believe that beta-blockers should remain first line treatment in the primary prevention of variceal haemorrhage.

Acute variceal bleeding

Endoscopic therapy has been considered the mainstay of specific therapy for acute variceal bleeding. Endoscopic sclerotherapy has been shown to reduce bleeding and increase survival.[19] Several sclerosing agents have been examined (polidocanol 1-3%, ethanolamine oleate 5% etc). There is no evidence that any one sclerosant can be considered the optimal for injection. Also there is no strong evidence suggesting that either intravariceal or paravariceal injection technique is better.[20] However, in case of rebleeding no more than two sessions of sclerotherapy within a 5-day period should be used to arrest variceal bleeding.[21]

Sclerotherapy has been assessed as follows: a) sclerotherapy combined with vasoactive agents versus vasoactive agents alone, b) sclerotherapy versus vasoactive

agents alone, c) sclerotherapy versus combination with drugs and d) sclerotherapy versus ligation. Overall combination has been proven to be more effective than monotherapy.[20] Furthermore, the early administration of somatostatin before endoscopy may improve the efficacy of combination therapy.[22]

Currently, emergency sclerotherapy has been challenged by vasoactive drug therapy.[23]Sclerotherapy was not superior to terlipressin, somatostatin, or octreotide in terms of rebleeding, blood transfusions, death and adverse events [risk differences and confidence intervals (CIs) were as follows: failure to control bleeding, -0,03 (-0,06 to 0,01); mortality, -0,035 (-0,07 to 0,008); adverse events, 0,08 (0,02 to 0,14). Mortality risk difference was -0,01 (-0,07 to 0,04) in good-quality trials and -0,08 (-0,14 to -0,02) in poor-quality trials]. The authors concluded that available evidence does not support emergency sclerotherapy as the first-line treatment; endoscopic therapy might be added only in pharmacologic treatment failures. However, the conclusion remains debatable.[24]

Endoscopic variceal ligation has been recently considered to be equal or superior to sclerotherapy in this setting.[25,26] As placement of the banding device requires extubation following the diagnostic endoscopy and then reintubation, this may increase the number of complications and the length of procedure. In addition, the insertion of the banding device in the tip of the endoscope reduces the optical view and may adversely affect the efficacy of endoscopic therapy.

According to the Baveno IV consensus in Portal Hypertension a) endoscopic therapy is recommended in any patient who presents with variceal bleeding, b) EVL is recommended although sclerotherapy may be used if ligation is technically difficult, c) combination of endotherapy with vasoactive drugs is preferable particularly when administration of drugs started early, before endoscopy.

During acute bleeding episodes high portal pressure has been shown to associate with poor prognosis. Recently a study comparing the effects of endotherapy (EIS or EVL) on hepatic venous pressure gradient (HVPG) during acute bleeding was carried out.[27] A significant increase was observed in mean portal pressure (20,7 mm Hg +/- 4,4 SD and 21,5 mm Hg +/- 4,5 SD, respectively, p <0,0001) immediately after treatment (time 0) as compared with pretreatment (18,1 +/- 4,5 and 18,1 +/- 4,0) in both groups. However, HVPG in the EVL group returned to baseline values within 48 hours after treatment, while in the EIS group it remained high during the 120-hour study period (p <0,0001) and was associated with higher rebleeding rate. Therefore, it seems that during acute variceal bleeding patients receiving EIS need vasoactive drugs for 5 days, while those who had undergone EVL might need drugs for only 2 days. Further clinical investigation is necessary in order to confirm the above important observation.

Secondary prevention

Patients surviving the first episode of variceal bleeding are at very high risk of recurrent bleeding (>70% at one year) and death (30-50%).[28]

Metanalysis of randomized trials showed that sclerotherapy reduced both the rebleeding rates (OR, 0,63 [95% CI, 0,49-0,79]) and mortality (OR, 0,77 [95% CI, 0,61-0,98]) compared to no treatment,whereas there was no difference between sclerotherapy and drugs (rebleeding OR, 0,88 [95% CI, 0,58-1,32]) - mortality (OR, 0,95 [95% CI, 0,58-1,32]). Comparing EIS plus drugs to EIS alone there was statistically significantly less rebleeding in the combined treatment arm (OR, 0,54 [95% CI, 0,34-0,86]) and fewer deaths (OR, 0,65 [95% CI, 0,43-0,97]) (20).There was no difference between long term EVL and drugs (rebleeding (OR 0,966, 95% CI 0,66-1,41) - mortality (OR 0,72, 95% CI 0,47-1,1). Band ligation seems to be superior to sclerotherapy as it is associated with lower rebleeding rates (OR, 0,53 [95% CI, 0,42-0,67]), and mortality (POR, 0,77 [95% CI, 0.59-0.99]) as well as complications (OR, 0,29 [95% CI, 0,19-0,44]).[20]

The aim of a recently published trial[29] was to compare the efficacy of EVL combined with nadolol versus EVL alone as secondary prophylaxis for variceal bleeding. The variceal bleeding recurrence rate was 14% in the EVL plus nadolol group and 38% in the EVL group (p = 0.006). After a median follow up of 16 months no difference in mortality rates between the two groups was observed. Authors concluded that a combination of nadolol with EVL reduces the incidence of variceal rebleeding compared with EVL alone.

Histoacryl is highly effective in controlling active bleeding. In a randomized trial endoscopic histoacryl obliteration was compared with propranolol in the secondary prevention of esophagogastric variceal bleeding. There was no difference in rebleeding or survival, but there were more complications with the adhesive injection.[30]

Transjugular intrahepatic portosystemic shunt (TIPS) has been used to prevent variceal rebleeding. In a recent meta-analysis (11 randomized trials, 811 patients), in

patients with variceal bleeding, TIPS compared with endoscopic treatment reduced the rebleeding rate, but did not improve survival and increased the incidence of encephalopathy in a period of 1 to 2,5 years. Therefore, TIPS cannot be recommended as the first choice treatment for prevention of variceal rebleeding.[31]

Guidlines based on the recent recommendations at the Baveno IV Consensus Workshop include: a) In patients who have not received primary prophylaxis: Beta-blockers, EVL or both should be used for prevention of recurrent bleeding. A combination of beta blockers and EVL is probably the best treatment, but more trials are needed, b) In patients with cirrhosis who are on beta-blockers for primary prevention and bleeding, band ligation should be added, c) In patients who have condraidications or intolerance to beta blockers, EVL is the treatment of choice and d) In patients who fail endoscopic and pharmacological treatment: TIPS or surgical shunts are effecive for those with Child class A/B. Transplantation should be considered for patients with Child class B/C (TIPS may be used as a bridge to transplantation).[5]

Gastric varices

Gastric varices represent a significant challenge for the gastroenterologist/endoscopist since they are serious complications of portal hypertension and are more difficult to control, especially through endoscopy. In the primary prevention setting there is on absence of specific data. In acute bleeders endoscopic therapy with tissue adhensive (e.g. N-butyl-cyanocrylate) is recommended. In secondary prevention the recommendations are: a) Patients who have bled from isolated gastric varices type I (IGV 1) or gastro-esophageal varices type 2 (GOV 2): N-butyl-cyanocrylate, TIPS or beta-blockers and b) Patients who bled from gastro-esophageal varices type I (GOV 1): N-butyl-cyanocrylate, band ligation or beta blockers.[5]

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